Inbred Strains of Rats: SHR

SHR

Inbr. F70 (NIH 1989).

Colour: Albino.

Genet. *c*.

Origin: Okamoto 1963 from outbred Wistar Kyoto rats. Bred from a male with mild hypertension, mated with a female with high blood pressure. Brother x sister mating with continued selection for high blood pressure (Okamoto 1969, Okamoto et al 1972). A number of sublines have been developed with a tendency to develop cardiovascular lesions and stroke (see particularly SHRSP) (Nagaoka et al 1976), and hypercholesterolemia (Yamori 1984). For a recent review see Yamori, (1994). However, there is no evidence for substrain differentiation among SHR stocks from the major commercial suppliers in the USA both respect to phenotype and DNA fingerprints (Blizard et al, 1991).

Strain WKY, developed from the same base populations is sometimes used as a normotensive control, though its use as such must be questioned as it differs at many genetic marker loci (Festing and Bender 1984, and see also strain WKY). Stelzin et al (1992) found that SHR and WKY shared only 50% of their DNA fingerprint bands, whereas SS and DS shared about 80% of bands. Most authorities suggest that WKY alone is not a good control strain, and that for most comparative studies several normotensive strains should be used.

There is an extensive literature on the characteristics of SHR. DeJong (1984) provides a useful comparative review of this and other hypertensive strains, and there are regular symposia on hypertensive rat strains (see J. Hypertension 4(suppl):S1-S541, 1986, and Jpn. Heart J. 28:567-648).

Characteristics.

High blood pressure (2/23), reaching 171_2.0 (SEM) mmHg at 10 weeks of age (Tanase et al 1982). According to Yamori (1984), the rats develop hypertension spontaneously without exception at the age of 7-15 weeks. There is a systolic blood pressure plateau of about 200 mmHg. The genetic basis is polygenic, with at least three major genes involved (Tanase and Suzuki 1971, Yen et al 1974). There is a high incidence of cardiovascular disease (Okamoto et al 1973), but a low incidence of stroke which can be increased to about 30% with chronic stress (Yamori 1984). Alloxan diabetes further increases blood pressure, but the animals

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respond to anti-hypertensive drugs (Okamoto 1969). Yamori states that SHR rats show a functional increase in peripheral vascular resistance, which mostly depend on neurogenic mechanisms which probably originate in a disorder of central blood pressure regulation. The blood pressure *per se* and increased neurogenic tone accelerate cardiovascular protein synthesis and induce structural vascular changes which contribute to the maintenance of the hypertension. Studies on cultured vascular smooth muscle suggest a genetic predisposition to hyperplastic growth of these cells and its stimulation by ß-adrenergic mechanisms. According to Dietz et al (1984) there is an abnormality of intracellular electrolyte balance with increased intracellular sodium and calcium concentration. Grobecker et al (1975) found that in young SHR rats the plasma levels of both noradrenaline and dopamine-ß-hydroxylase were increased over control WKY rats, but total catecholamines were not significantly different. Catecholamine content of the adrenals was reduced. Circulating thyrotrophin levels were markedly elevated over two control strains (Werner et al 1975). There was a reduced ^{131}I metabolism and increased thyroid weight relative to Wistar controls (Fregley 1975). Reduction of dietary vitamin E prevents the development of hypertension, possibly due to a significant increase in prostaglandin catabolism (Pace-Asciak and Carrara 1979). Caloric restriction lowers blood pressure (Young et al 1978). Environmental and dietary factors cna influence the degree of hypertension (Yamori et al 1979, 1986). A high (8%) salt diet increased systolic blood pressure, but not so much as in strain SS/Jr (Adams and Blizard, 1991). A polymorphism in the heat shock protein 70 (hsp70) mapping in the RT1 complex was found to be associated with variation in blood pressure of 15mm Hg among recombinant inbred strains (Hamet et al, 1992). Strain is significantly more sensitive to the hypotensive effects of GABA than normotensive Sprague-Dawley or WKY rats, with evidence that the effects are mediated by the brain angiotensin system (Roberts et al, 1993). Plasma renin and angiotensin II levels are not elevated (Cambell et al, 1995). Glucose turnover in lean and obese (carrying the fatty gene) SHR rats has been described by Berdanier et al, (1993). There is reduced cancellous bone mass in SHR compared with WKY (Wang et al, 1993). The Y-chromosome of SHR increases blood pressure when backcrossed to strain WKY for 11 generations (Ely et al, 1993). There is a deficit in visual acuity at 40-66 days, prior to the onset of hypertension, and it is particularly marked in the blue spectrum (Rogers et al, 1993).

Low 10-week body weight in males (2/23) (Tanase et al 1982). High relative heart weight in 10-week old males (22/23) (Tanase et al 1982). SHR rats express insulin resistance, and are a suitable model for insulin resistance and essential hypertension in non-obese humans (Swislocki and Tsuzuki, 1993).

Have fewer glomeruli than WKY rats, but they are of similar size, resulting in a reduced glomerular volume. This is consistent with the hypothesis that the kidney plays an important role in hypertension (Skov et al, 1994). Foetal but not placental weight is reduced compared

with WKY (Johnston, 1995).

Genetically resistant to the induction of mammary tumours by dimethylbenz(a)anthracene due to a blockade of tumour promotion (Harris et al, 1994).

Roba (1976) concluded that the strain is a suitable model for screening anti-hypertensive drugs.

The "Committee on the care and use of hypertensive rats (1976)" has issued guidelines for the breeding and care of this strain.

A congenic strain carrying the "corpulent" gene (cp), an allele of fatty (*fa*) has been developed and is described by Michaelis and Hansen (1990). Homozygotes develop both metabolic and histopathologic characteristics associated with non-insulin-dependent diabetes mellitus (type II) in humans. It is unique among rat strains in that glucose intolerance is expressed in both sexes. A similar strain, in which the fatty (*fa*) gene has been backcrossed to SRH for five generations has been described by Chanh et al (1988) Homozygous fatty rats were heavier than fa/+ litter mates, with blood pressure elevated above that of SHR animals. Blood glucose content was not different from SHR, but plasma triglycerides were increased by more than 500% from an early age.

SHR rats are hyperactive and may be a useful model for childhood hyperkinesis and attention-deficit hyperactivity disorder (Sagvolden et al, 1993).

SHROB

Origin: Reserved symbol for strain in development by Dr. Richard Koletsky.

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INBRED STRAINS OF RATS
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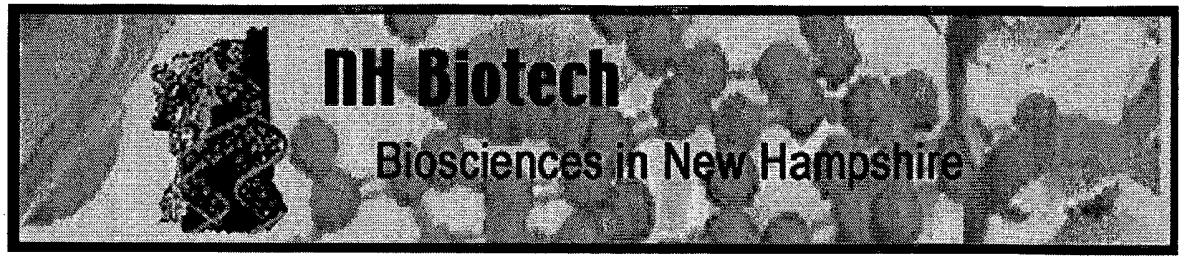

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Inbred Strains of Rats: SHRSP

SHRSP

Inbr. F59.

Colour: Albino,

Genet. *c*.

Origin: The A1-sb and A3 substrains of SHR which had been bred as parallel lines from F20 to F36 were crossed (?) and further inbred with selection of offspring of parents that died of stroke (Okamoto et al 1974, 1986, Yamori 1984). To NIH in 1976, and designated SHRSP/A3N. Pathophysiology reviewed by Volpe and Rabbatu (1994).

Characteristics.

High blood pressure (1/23), reaching 187_2.2 (SEM) mmHg at 10 weeks of age (Tanase et al 1982). The hypertension has been extensively reviewed by Yamori (1984) as follows: Cerebral hemorrhage or infarction in 82% of males over 100 days of age and 58% of females over 150 days of age. The main sites are the anteriomedial and occipital cortex, and the basal ganglia. They have a higher blood pressure (by 40-50 mmHg) than SHR, and in both strains the blood pressure is maintained by higher peripheral vascular resistance which at first is due to neurogenic vasoconstriction. Membrane changes may be involved. Regional cerebral blood flow is reduced, especially in areas of the brain fed by recurrent branches. Body weight is lower than in SHR. Signs of stroke include piloerection, hyperkinesis, hyperirritability, aggressiveness and motion disturbance.

Stroke in these rats is affected by both genetic and environmental factors. Hypertension, vascular wall changes, and salt metabolism as well as a reduction in cerebral blood flow are important systemic and local factors in the stroke. Stroke is prevented by antihypertensive agents and the incidence can be modified by diet, being reduced by the inclusion of fish and vegetable oils. Excessive salt intake increases hypertension and its complications. A high protein diet attenuated the development of severe hypertension, and counteracted the adverse effect of salt. High relative heart weight in 10-week old males (23/23) (Tanase et al 1982). Liver gangliosides are of the b-type (cf WKAH) (Kasai et al 1993). There was no evidence for co-segregation between blood pressure and the angiotensinogen locus, or any other phenotypic parameter in crosses involving WKY (Hubner et al, 1994, 1995).

Hubner N., Kreutz R., Takahashi S., Ganten D., and Lindpaintner K.

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